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Late-Onset Warfarin-Induced Skin Necrosis: Case Report and Review of the Literature

D.W. Essex,* S.S. Wynn, and D.K. Jin

Department of Internal Medicine, Division of Hematology/Oncology State University of New York, Health Science Center at Brooklyn, Brooklyn, New York

Warfarin-induced skin necrosis is a rare complication of therapy with warfarin or other coumarin derivatives. When it occurs it usually appears 3 to 6 days after initiation of therapy and almost always between days 1 and 10. We report a case of late-onset (16 days after initiation of therapy) warfarin-induced skin necrosis and review the literature on this rarely reported variant of warfarin-induced skin necrosis. The skin lesion in our patient was not associated with either deficiency of protein C or resistance to activated protein C. Am. J. Hematol. 57:233–237, 1998. © 1998 Wiley-Liss, Inc.

Key words: warfarin; late-onset; skin necrosis; resistance to activated protein C

INTRODUCTION

Warfarin-induced skin necrosis almost always occurs by day 10 after institution of warfarin therapy [1,2]. We report a case of late-onset warfarin-induced skin necrosis occurring 16 days after the initiation of warfarin therapy. There are 6 previous reports of late-onset warfarin-induced skin necrosis (see Table I). Potential causes of this entity include warfarin being inadvertently stopped and then restarted, diseases affecting synthetic function of the liver, and possibly the interaction of drugs with warfarin metabolism.

The etiology of the warfarin-induced skin necrosis, while not completely clear, is thought to occur from a transient imbalance in the procoagulant-anticoagulant system relating to a rapid decrease in the anticoagulant protein C during warfarin therapy [3]. In fact, warfarin-induced skin necrosis may be associated with hereditary protein C deficiency [4,5]. Resistance to activated protein C has been found in about 5% of the general population and in 20–60% of patients with deep venous thrombosis [6]. Since most cases of warfarin-induced skin necrosis, including our patient, are not associated with deficiency of protein C, we tested if resistance to activated protein C could be implicated in our patient.

CASE REPORT

A 34-year-old non-obese woman with a 7-year history of systemic lupus erythematosus developed a left lower extremity thrombosis that, on duplex ultrasonography, extended to her popliteal vein. She was treated with standard heparin therapy and started on a 10 mg warfarin/day for 4 days, which was decreased to 5 mg/day before discharge from the hospital. She claimed daily compliance with warfarin and on day 14 of warfarin therapy her PT was 17.5 sec (normal 10.7–12.7 sec) and INR 2.87. On day 16 of warfarin therapy, localized pain began in her thighs and legs as well as her left upper arm. Petechiae soon developed in these areas. Over the ensuing hours these lesions changed to large blue-black ecchymotic areas with several bullae and an erythematous halo that was tender and warm to touch (Fig. 1). Her medications at the time were prednisone (100 mg/day) and she noted taking 3 tablets (400 mg) of ibuprofen beginning the night prior to the onset of symptoms. Laboratory examination revealed a white blood cell count (WBC) of 2,900/μl, a hemoglobin of 8.3 g/dl, and a platelet count of 111,000/μl. The prothrombin time (PT) was 15.8 sec (normal 10.7–12.7 sec; INR 2.2) and the partial thromboplastin time (PTT) 28.8 sec (normal 25–32 sec). SGOT, alkaline phosphatase, total and direct bilirubin were normal. The LDH was 257 IU/l, total protein 6.2

*Correspondence to: Dr. David Essex, Department of Biochemistry, State University of New York, Health Science Center at Brooklyn, 450 Clarkson Avenue, Brooklyn, NY 11203.

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TABLE I. Characteristics of Reported Cases of Late-Onset Warfarin-Induced Skin Necrosis*

Case	Sex/age	Time of onset	Thrombosis	Location of necrosis	Oral anticoagulant	Prothrombin time at time of necrosis	Associated conditions	Medications	Reference
1	F/36	Day 15	DVT	Breast, thigh	Acenocoumarol	Quick test 17% (normal 70–100%; therapeutic 15–25%)	Therapeutic abortion	—	[8]
2	F/34	Day 16	DVT	Arm, thighs, legs, feet	Warfarin (5 mg/day)	15.8 sec (normal 11–12.5 sec)	SLE, antiphospholipid antibodies	Prednisone, ibuprofen	Present case
3	F/45	Day 17	DVT	Knee	Warfarin (5 mg/day)	18 sec (therapeutic)	Protein C deficiency, concurrent DIC	—	[9]
4	F/59	3 months	Left ventricle	Thigh, calves	Warfarin	14.7 sec (control 11.5 sec)	Heart failure, coronary artery disease, hypertension, diabetes	Digoxin, furosemide, isosorbide dinitrate, cephalexin	[10]
5	M/25	17 months	DVT	Buttocks	Warfarin (10 mg/day)	22 sec (normal 11–13 sec)	Klinefelter's syndrome, mononucleosis	Testosterone	[11]
6	F/70	3 years	DVT, PE	Thighs, breast	Acenocoumarol	30 sec (control 20 sec)	Surgery for retinal detachment, flu-like symptoms	Salicylate	[12]
7	F/57	Recurrent	CVA	Buttocks, calves, dorsal aspect of feet	Phenprocoumon	INR >5.4 (on each occasion)	Heart failure, mitral valve incompetence, atrial fibrillation, diabetes	Digoxin, furosemide, spironolactone, insulin	[13]

*DVT, deep venous thrombosis; PE, pulmonary embolism; CVA, cerebral vascular accident; SLE, systemic lupus erythematosus; DIC, disseminated intravascular coagulation; INR, international normalized ratio.

Fig. 1. Skin necrosis. The lesions began by a painful sensation, followed by petichea, which coalesced to ecchymosis over several hours. The edge of the lesion was erythematous and warm to touch.

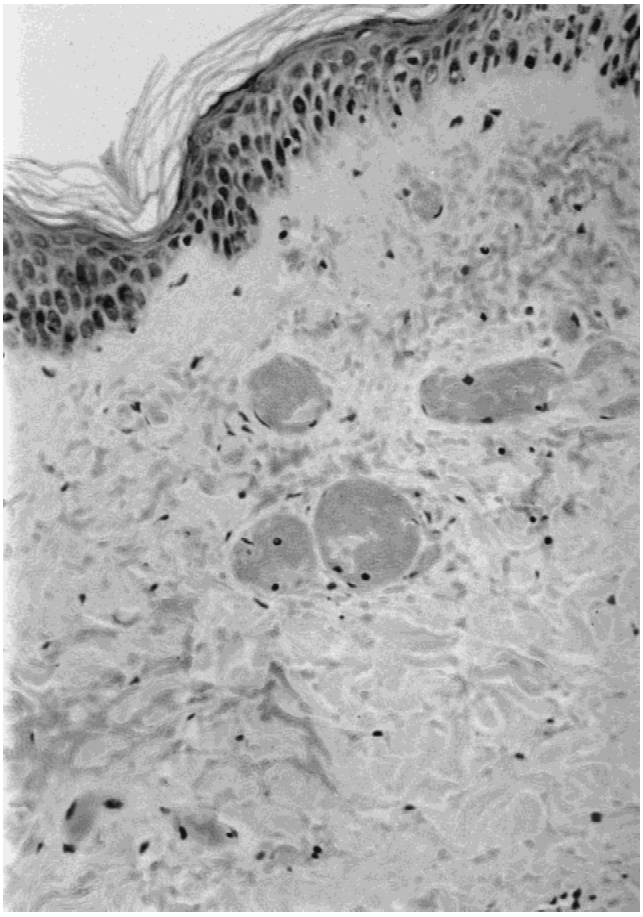

Fig. 2. Section of the skin biopsy showing thrombosis of superficial dermal capillaries.

g/dl, and albumin 2.7 g/dl. A diagnosis of warfarin-induced skin necrosis was made and the warfarin was discontinued, intravenous heparin started, and subcutaneous vitamin K administered. Skin biopsy done on admission at the periphery of a lesion was consistent with warfarin-induced skin necrosis, revealing subepidermal hemorrhage with adjacent epidermal necrosis and congestion and thrombosis of superficial dermal capillaries (Fig. 2). There was no vasculitis noted in any of the sections. Skin grafting was recommended for the skin lesions but the patient refused (there has subsequently been poor, but adequate, healing). The patient was treated with low-molecular-weight (LMW) heparin (Lovenox) at a dose of 1 mg/kg every 12 hr. Four months after the original thrombosis, she presented with tenderness and swelling of the right lower extremity, about 10 days after she self-discontinued the LMW heparin. Duplex ultrasonography demonstrated a new deep venous thrombosis. Another LMW heparin preparation (Fragmin, which she claimed caused less discomfort with injection) was started at 2,500 U subcutaneously every 12 hr and was continued uneventfully for 12 months (a higher dose of Fragmin is recommended for treatment of deep venous thrombosis but was not available in single vial injections and the patient refused using multiple vials).

MATERIALS AND METHODS

Functional protein C and protein S levels were assayed with the Staclot protein C or S kit (Diagnostica Stago, Asnieres-Sur-Seine, France). Antithrombin III levels were measured with the Stachrom ATIII (Diagnostica Stago). The Dilute Russell's viper venom time test was done using the DVVtest kit (American Diagnostica Inc., Greenwich, CT). Anticardiolipin antibodies were measured by a commercial ELISA kit (READS Medical Products, Inc., Westminister, CO). Resistance to activated protein C was assayed using the Coatest APC-Resistance-C (Chromogenix, Molndal, Sweden).

RESULTS

Evaluation for possible hypercoagulable states, done over 2 weeks after the initial hospitalization (when the heparin had been held), showed a functional protein C level of 81% (normal range 70–130%), functional protein S of 120% (normal range 65–140%), and an antithrombin III level of 110% (normal range 80–120%). The dilute Russell's viper venom time test ratio was 1.27 (normal range 0.76–1.23). Anticardiolipin antibodies were 58 GPL U for IgG (normal <23 GPL U) and 7 GPL U for IgM (normal <11 MPL U). The resistance to activated protein C ratio was 2.6 (normal range 2.0–4.0).

DISCUSSION

In 115 cases from the two largest literature reviews on warfarin-induced skin necrosis, the first symptoms of skin injury always appeared within 10 days of therapy with the peak incidence (83–90% of all cases) being between days 3 and 6 [1,2]. This is because the skin necrosis is likely related to a transient imbalance in the proteins of the procoagulant-anticoagulant systems occurring during the initial phase of anticoagulation before steady-state levels of these proteins are reached. The occurrence of warfarin skin necrosis in our patient on day 16 of warfarin administration was well after the effect of warfarin on vitamin K-dependent clotting factors should have reached peak anticoagulant activity (by 72–96 hr) [3].

There are reports of late-onset warfarin-induced skin necrosis occurring after 15 days, 17 days, 3 months, 17 months, and 3 years of warfarin therapy (see Table I). The possibility exists in some of these reports that oral anticoagulation was inadvertently stopped and then restarted prior to the necrosis. Our patient claimed daily compliance with warfarin and had a therapeutic INR 2 days prior to the skin necrosis. Also, some of these patients were hospitalized and on monitored anticoagulant therapy with therapeutic levels of anticoagulation (cases 1 and 3). Therefore, other causes of late-onset warfarin-induced skin necrosis must be considered. Interestingly, two of the cases (4 and 7) were associated with evidence of biventricular heart failure [10,13]. One of these patients had 5 repeated episodes of warfarin-induced skin necrosis, each in association with over-anticoagulation occurring during periods of congestive heart failure [13]. It was hypothesized that a procoagulant-anticoagulant imbalance occurred during these periods secondary to right heart failure affecting the synthetic function of the liver. This is possible since the anticoagulant protein C synthesized by the liver has a short half-life similar to that of factor VII, and its blood level would decrease in liver disease before that of the procoagulant factors II, IX, and X.

It is well known that warfarin and other coumarin derivatives are highly protein-bound agents. The possibility exists that some drugs may displace albumin-bound warfarin, or in some other way alter warfarin metabolism, resulting in a transient procoagulant-anticoagulant imbalance. Cameron et al. have reported a case of oral anticoagulant-induced skin necrosis occurring after 3 years of therapy that was associated with ingestion of sodium salicylate (4 g/day) for 4 days [12]. Our patient ingested ibuprofen and in the preceding hours prior to the onset of warfarin-skin necrosis and non-steroidal anti-inflammatory agents, including ibuprofen, displaced warfarin from albumin in vitro [14], raising the possibility of a potential drug interaction between ibuprofen and warfarin. However, ibuprofen and other propionate derivatives do not normally alter the effects of warfarin on the prothrombin time [15,16], and whether this association was causal is unclear. In summary, possible causes of late-onset warfarin-induced skin necrosis include inadvertent discontinuation and then restarting of warfarin, a sudden decrease in synthetic function of the liver, and drug interactions.

Three prior reports on warfarin-induced skin necrosis in association with antiphospholipid syndrome have been documented. One of these patients had concurrent protein C deficiency [17] while the other two had an acquired protein S deficiency [18]. The skin necrosis in these patients occurred 3 to 4 days after the initiation of anticoagulation therapy. The present case is otherwise unique because our patient had normal functional protein C and S levels; therefore, the warfarin-induced skin necrosis in our patient could not be ascribed to these deficiencies.

The exact etiology of warfarin-induced skin necrosis is unclear. The involvement of protein C in warfarin skin necrosis has been implicated because protein C synthesis is blocked by warfarin and protein C activity decreases rapidly following warfarin treatment [7]. Patients with heterozygous protein C deficiency are at greater risk [4,5,19] and replacement therapy with protein C appears to block the progression of the lesions and aid in healing [20,21]. These types of situations might be expected to worsen by the factor V Leiden mutation in which an arginine residue is mutated to a glutamine, abolishing a cleavage site involved in factor V inactivation [22]. Although this abnormality is commonly found in patients with hypercoagulable states, our patient did not have resistance to activated protein C, suggesting that resistance to activated protein C may not be a major etiologic factor in late-onset warfarin-induced skin necrosis, although this question can only be addressed with studies of more patients.

In addition to the present case, LMW heparin has previously been used successfully for the treatment of venous thrombosis in other patients with warfarin-induced

skin necrosis [9,23]. While osteoporosis is a common side effect of chronic administration with standard heparin, recent studies have demonstrated that LMW heparin at therapeutic levels results in less calcium release from bone [24] and less fractures [25]. This is especially important when patients are concomitantly receiving chronic steroid therapy that can also induce osteoporosis. Other advantages of LMW heparin over standard heparin include a lower risk of heparin-induced thrombocytopenia and it is unnecessary to monitor the PTT. Since there is possibility of recurrence of warfarin-induced skin necrosis with reinstitution of warfarin therapy, we recommend LMW heparin as a treatment for this condition.

NOTE ADDED IN PROOF

Another report of late-onset warfarin-induced skin necrosis occurring in a 55-year-old female on day 46 of therapy recently came to our attention [26].

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